

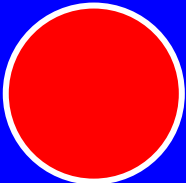
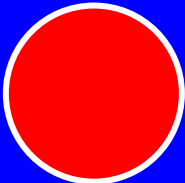
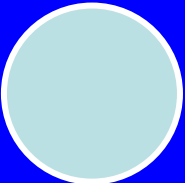
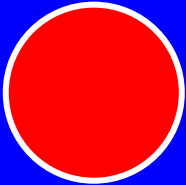
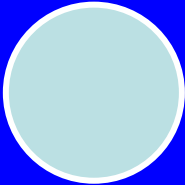
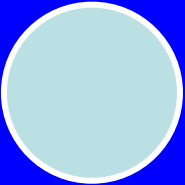
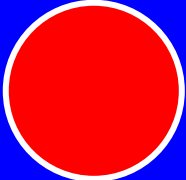
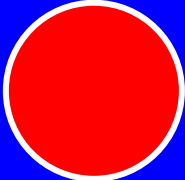
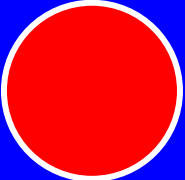
New Strategies for TB Treatment?

Münchenwiler, March 22, 2007

Hans L Rieder

How to define drug resistance?

Reproducibility versus Validity

Patient	Lab A	Lab B	Comment
			Irreproducible, valid / invalid by chance
			Reproducible, invalid
			Reproducible and valid

Global Project on Surveillance of Anti-Tuberculosis Drug Resistance:

Definition of Drug Susceptibility based on Reproducibility, not Validity

“...Results from all laboratories will be compared to the judicial results, based on the consensus of the participants. **When there is no true consensus result, i.e. less than 80% concordance susceptible / resistant, this susceptibility report will be excluded for final performance analysis,** and analysed separately, using clinical and genotype information...”

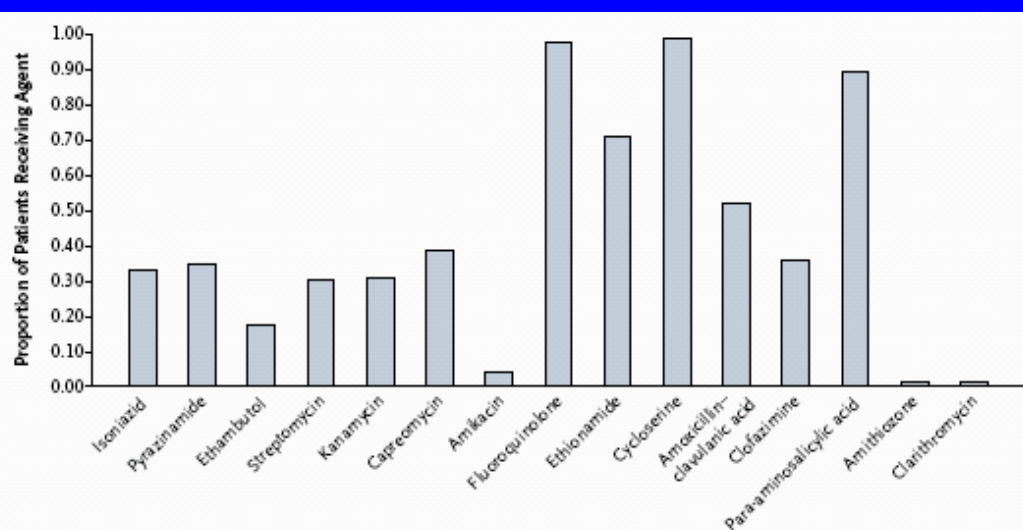
World Health Organization. Protocol. Quality assurance programme for drug susceptibility of Mycobacterium tuberculosis in the network of supranational tuberculosis laboratories (SRLN). Thirteenth round of proficiency testing, 2006. Dated: August 31, 2006

To get laboratories agree amongst themselves on average...
 ...an important component, but not the only one that counts

Drug	Recommended test concn	
	In BACTEC 460	On Middlebrook 7H10 agar
Capreomycin	1.25	10.0
Cycloserine	— ^a	—
Ethionamide	1.25	5.0
Kanamycin	5.0	5.0
Amikacin	1.0	4.0
Clofazimine	0.5	1.0
Ofloxacin	2.0	2.0
Rifabutin	0.5	1.0

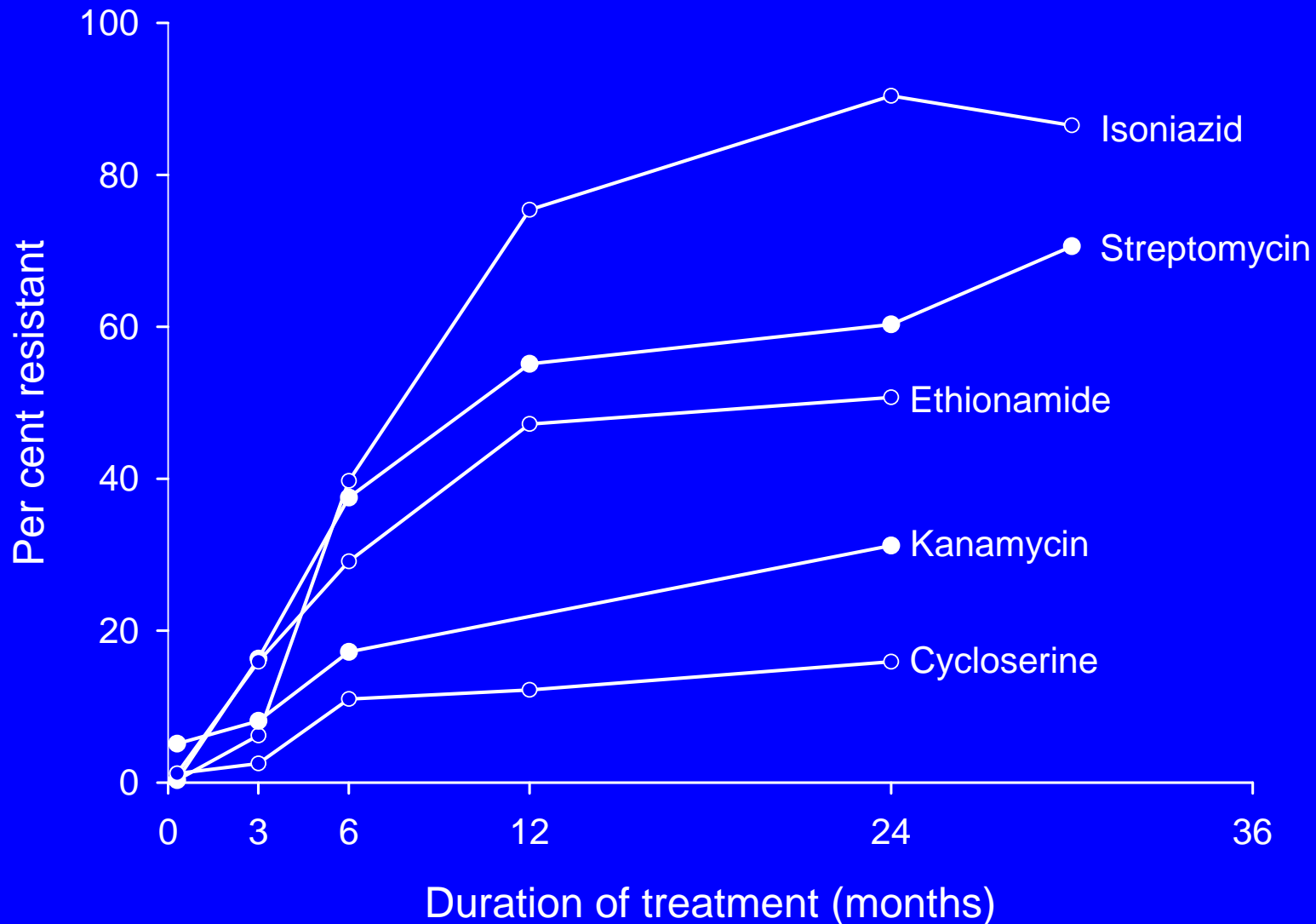
*Pfyffer G E, et al. J Clin Microbiol
 1999;37:3179-86*

...applied to clinical practice, 75 patients on 55 different regimens

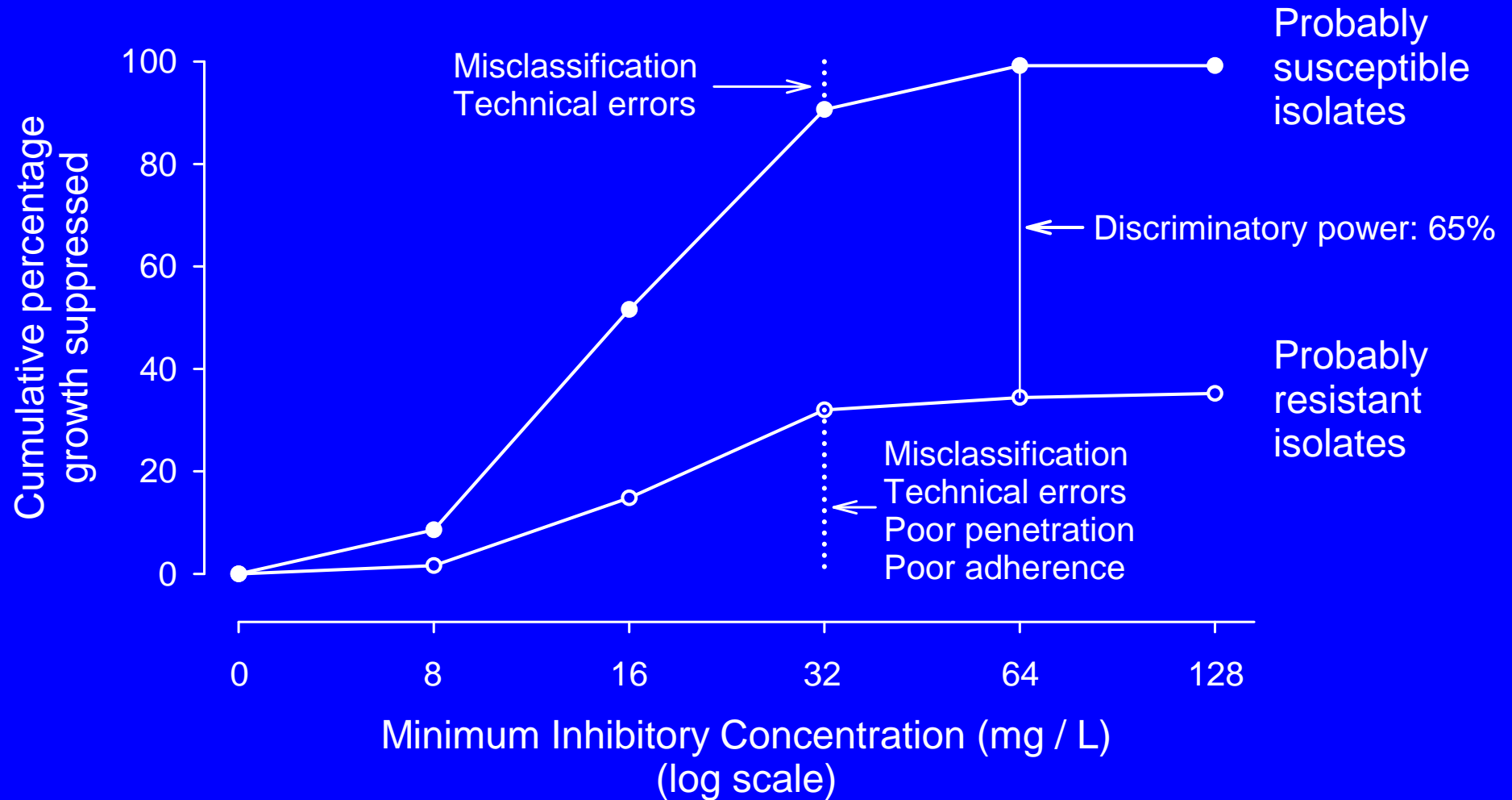


*Mitnick C, et al. N Engl J Med
 2003;348:119-28*

Proportion of Strains Cultured from Resected Lungs Resistant to Anti-Tuberculosis Drugs, as a Function of Duration of Treatment Strain Containing no Susceptible Bacilli



Determination of Critical Concentration for Rifampicin in Korea



Data courtesy: Kim SJ, Korean Institute of Tuberculosis
Unpublished lecture notes, Hanoi, September 1, 2000

Different approaches to anti-MDR treatment...

Approach

Author

4 to 6 drugs based on DST

ATS, CDC

5 to 9 drugs based on DST

PIH

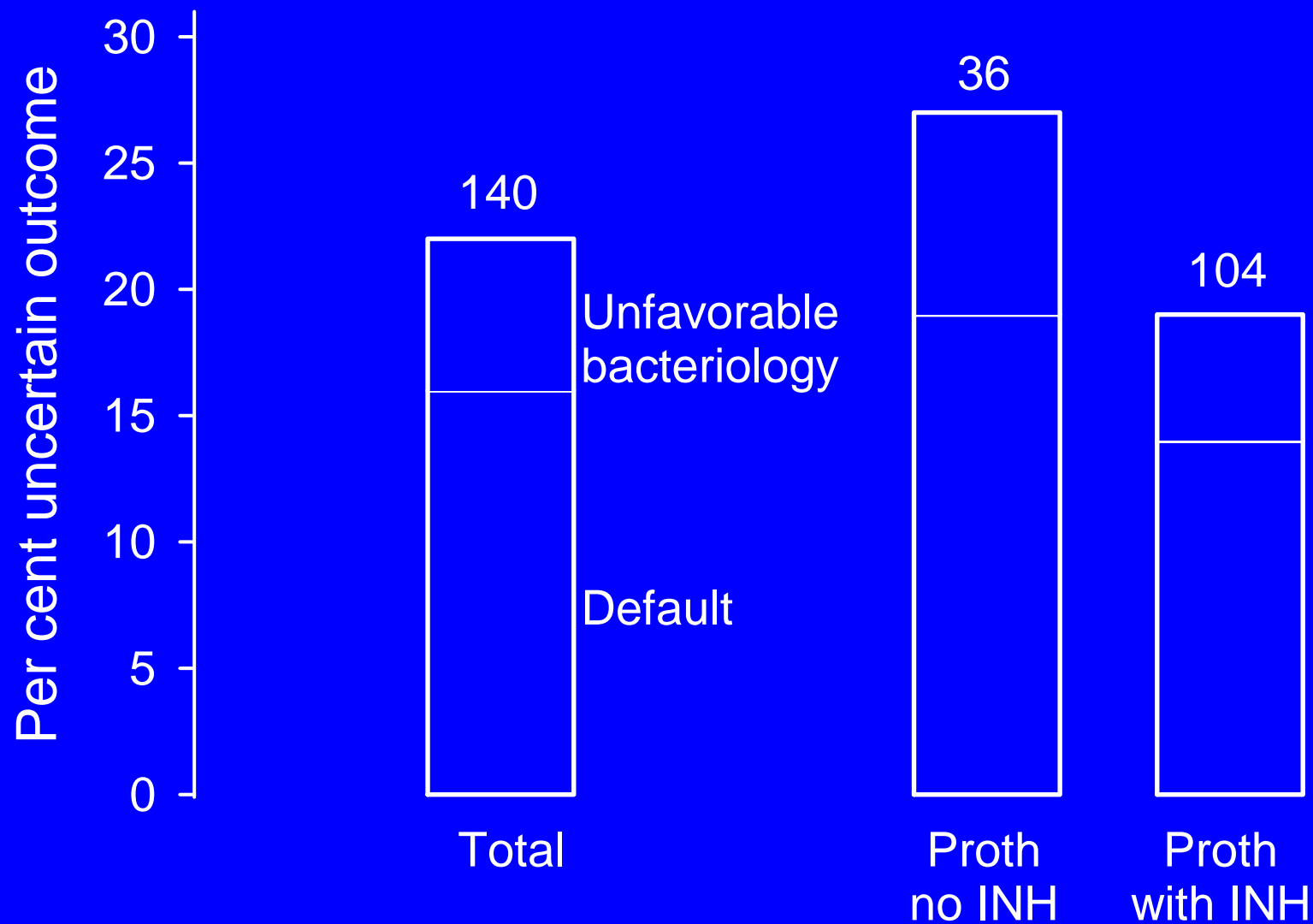
3 drugs based on country history

Cambrero

Short, low-toxicity combination
based on country history

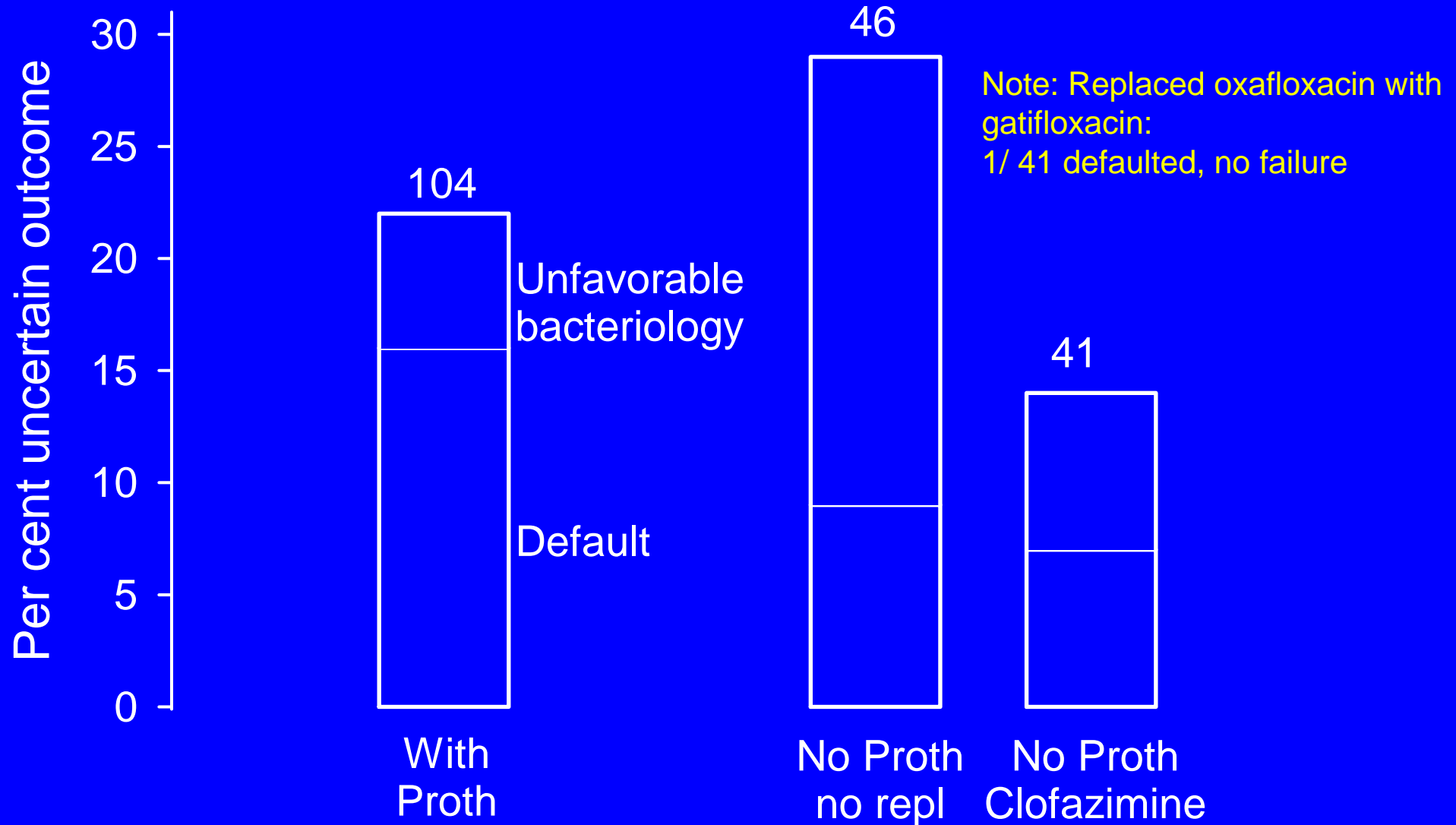
Van Deun

Unfavorable Outcome of MDR with Ofloxacin Throughout, Stratified by Isoniazid Use



*Data courtesy: Van Deun A, unpublished data, Nov 2006
Damien Foundation, Bangladesh*

Unfavorable Outcome of MDR with Ofloxacin Throughout, Stratified by Prothionamide Use



Data courtesy: Van Deun A, unpublished data, Nov 2006
Damien Foundation, Bangladesh

Clinical Trial of New Classes for 9 and 15 Months?

- o Minimum harm (but possibly benefit) from always including isoniazid (plus ethambutol?)
- o Fluoroquinolone (gatifloxacin or better)
- o Oxazolidinone (e.g. eperezolid, linezolid, PNU-100480)
- o Diarylquinoline (e.g., R07910)

Those who first produced isoniazid resistance,
were the first to produce MDR

Those who first produced MDR, now produce XDR

- Not a priority group for provision with new drugs,
perhaps rather the reverse...